

Myeloid cell leukemia-1 dependence in acute myeloid leukemia: a novel approach to patient therapy

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Keywords: AML; BCL-2; MCL-1; flavopiridol; alvocidib

Received: November 08, 2018

Accepted: December 16, 2018

Published: February 08, 2019

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ABSTRACT

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, affecting approximately 21,000 people annually (nearly 11,000 deaths) in the United States. B-cell lymphoma 2 (BCL-2) family proteins, notably myeloid cell leukemia-1 (MCL-1), have been associated with both the development and persistence of AML. MCL-1 is one of the predominant BCL-2 family members expressed in samples from patients with untreated AML. MCL-1 is a critical cell survival factor for cancer and contributes to chemotherapy resistance by directly affecting cell death pathways. Here, we review the role of MCL-1 in AML and the mechanisms by which the potent cyclin-dependent kinase 9 inhibitor alvocidib, through regulation of MCL-1, may serve as a rational therapeutic approach against the disease.

INTRODUCTION

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. According to the American Cancer Society, the incidence of AML has increased 1.7% per year from 2004 to 2013 [1]. In 2017 in the United States, it was estimated that AML affected approximately 21,000 people and resulted in nearly 11,000 deaths. Moreover, although death rates from other acute and chronic leukemias decreased by about 1% per year from 2005 to 2014, mortality rates remained consistent for AML [1]. AML is characterized by the infiltration of bone marrow, blood, and other tissues by poorly differentiated hematopoietic cells. It displays distinct clinicopathologic, cytogenetic, and genetic characteristics; these and other factors are used to categorize patients according to most appropriate treatment, prognosis, risk of resistance, or potential for treatment-related mortality [2–4].

Alterations in apoptotic pathways are common in human malignancies and, in certain cancers, essential for tumorigenesis and cancer maintenance [5]. In this context, B-cell lymphoma 2 (BCL-2) family proteins, notably myeloid cell leukemia-1 (MCL-1), are known for their role in both the development and persistence of AML [6, 7], and are often associated with cancer-cell survival

and resistance to chemotherapy [8, 9]. Furthermore, as explored in detail in this article, gene expression analysis suggests that MCL-1 is one of the predominant BCL-2 family members expressed in samples from patients with untreated AML [10]. Here, we review the role of MCL-1 in AML and the mechanisms by which the potent cyclin-dependent kinase (CDK) 9 inhibitor alvocidib may serve, through regulation of MCL-1, as a rational therapeutic approach against the disease.

CURRENT AND NOVEL TARGETED THERAPIES FOR ACUTE AND CHRONIC LEUKEMIAS

Standard treatment for AML consists of intensive induction chemotherapy, followed by consolidation chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT) in patients with high-risk disease. Select groups of patients are offered lower-intensity therapy (eg, hypomethylating agents) or investigational therapy in a clinical trial [11]. Patients with AML have a poor prognosis, particularly older patients [1, 12–18]. Complete responses are achieved in only approximately 40% of patients aged 70 years or older compared with approximately 70% of patients aged 60 years or younger

[19]. Despite marked advances in understanding the biology and genetics of AML, therapeutic progress has been limited [1]. For the past 30 years, cytarabine and anthracycline-based induction chemotherapy has been the standard of care [20–23].

In recent years, multiple efforts have focused on the development of targeted therapeutics directed against relevant proteins (Table 1) [24–61]. These include approved agents such as the kinase inhibitor midostaurin for patients with FLT3 mutation-positive AML (Rydapt[®], Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA); the isocitrate dehydrogenase inhibitors (IDH) ivosidenib (Tibsovo[®], Agios Pharmaceuticals, Cambridge, MA, USA) and enasidenib (Idhifa[®], Celgene Corporation, Summit, NJ, USA and Agios Pharmaceuticals, Cambridge, MA, USA) for patients with IDH1 mutation-positive and IDH2 mutation-positive AML, respectively; and the CD33-targeted antibody-drug conjugate gemtuzumab (Mylotarg[™], Wyeth Pharmaceuticals, Philadelphia, PA, USA). Other agents under investigation in AML [62] include poly ADP-ribose polymerase inhibitors that may trigger irreparable DNA damage [63, 64]; epigenetic drugs that may modulate methylation, acetylation, and cell signaling and cycling [65]; and Aurora kinase inhibitors, which target the Aurora family of serine/threonine kinases, enzymes essential for multiple processes during mitosis, including chromosome alignment, centrosomal maturation, mitotic spindle formation, and cytokinesis [66–69]. Additional compounds have received orphan drug designation for the treatment of AML [70], including the histone deacetylase inhibitor pracinostat (MEI Pharma, San Diego, CA, USA) and the CDK9 inhibitor alvocidib (Tolero Pharmaceuticals, Lehi, UT, USA).

Alvocidib (also known as L86-8275, NSC 649890, and flavopiridol) is a semisynthetic flavonoid derived from rohitukine, an alkaloid isolated from a plant indigenous to India. Early studies described it as a potent compound capable of reversibly blocking cell progression at more than one point of the cell cycle, as addressed in this review [71].

CLINICAL STUDIES WITH ALVOCIDIB

Alvocidib was the first CDK inhibitor to enter human clinical trials [72]. Multiple preclinical [6, 73–77] and clinical [49, 78–85] studies have been conducted, leading to combination therapies that, based on the mechanism(s) of action of alvocidib, have shown clinical activity supporting further development. These include the addition of alvocidib to regimens containing cytarabine and mitoxantrone (ACM [formerly FLAM]) [81, 82, 84] and fludarabine/rituximab, investigated in a phase I trial in patients with mantle cell lymphoma, chronic lymphocytic leukemia (CLL), or indolent B-cell non-Hodgkin's lymphoma [83]. In fact, in earlier phase II trials, the ACM regimen showed an overall complete remission

rate of 67–80% in patients with newly diagnosed, poor-risk AML, with low rates of morbidity and mortality [81, 86, 87]. More recently, these observations were extended to a multicenter randomized phase II trial in adults with newly diagnosed AML with intermediate- and adverse-risk cytogenetics [84]. ACM led to higher complete remission rates than 7+3 (70% vs 46%; $p = 0.003$); this improvement persisted after 7+3 ± 5+2 (70% vs 57%; $p = 0.08$), further illustrating the efficacy of ACM induction in patients with newly diagnosed AML [84, 85]. Importantly, ACM was not associated with increased toxicity relative to 7+3, with similar rates of tumor lysis syndrome (TLS; 8% vs 7%, respectively). However, two ACM-treated patients compared with one 7+3-treated patient experienced early death due to TLS, and three grade 4 TLS toxicities were reported, all in patients treated with ACM [84].

Combination therapy with other targeted agents has also been studied. In a phase I trial, alvocidib was investigated in combination with the histone deacetylase inhibitor vorinostat in patients with relapsed, refractory, or poor prognosis acute leukemia or refractory anemia with excess type-2 blasts [49]. In this study, no objective responses were achieved, although 13 of 26 evaluable patients exhibited stable disease. The combination of alvocidib with vorinostat was well tolerated, with fatigue being the most common non-hematologic adverse event. No patient experienced TLS, but this study was designed to monitor and prophylactically treat TLS [49]. Alvocidib was also studied in combination with the proteasome inhibitor bortezomib in a phase I trial of patients with recurrent or refractory B-cell neoplasms [80] and as a bolus infusion in a similar patient population [79]. These studies showed that the regimen was clinically active in these patients and, importantly, the nonhybrid schedule regimen was recommended for subsequent studies [79, 80]. Based on preclinical findings that alvocidib potentiated imatinib-mediated cell death in human Bcr-Abl+ cells, a phase I trial of alvocidib plus imatinib in advanced Bcr-Abl+ leukemias was initiated [78]. These studies, along with others, led to the designation of alvocidib as an orphan drug in 2014 [70].

ALVOCIDIB AND CYCLIN-DEPENDENT KINASES: EFFECTS ON CELL CYCLE AND GENE EXPRESSION

One of the most relevant hallmarks of cancer cells is their ability to maintain proliferation, an effect directly associated with a deregulated cell cycle [5, 88]. Unconstrained proliferation secondary to the loss of cell-cycle regulation plays a key role in the initiation and progression of cancer. Early studies conducted to identify the mechanism(s) of action of alvocidib showed its inhibitory effects on cell-cycle progression [71, 89–91].

Progression through the cell cycle is monitored at cell-cycle checkpoints where potential defects in DNA

Table 1: Targeted-therapies for AML molecules***FMS-like tyrosine kinase 3 kinase inhibitors**

- Sorafenib (Nexavar[®]; Bayer Healthcare Pharmaceuticals Inc, Whippany, NJ, USA) [24–28]
- Midostaurin (Rydapt[®]; Novartis, East Hanover, NJ, USA) [29–31]
- Quizartinib (Daiichi Sankyo Group, Parsippany, NJ, USA) [32, 33]
- Crenolanib besylate (Arog Pharmaceuticals, Inc, Dallas, TX, USA) [34, 35]
- Gilteritinib (Astellas Pharma, Tokyo, Japan) [36]

Antibody-based therapies

- Gemtuzumab ozogamicin (anti-CD33; Mylotarg[™], Pfizer, New York, NY, USA) [37–39]
- IMGN779 (anti-CD33; ImmunoGen, Waltham MA, USA) [40]
- MCLA117 (bispecific anti-CLEC12A×CD3; Merus, Cambridge, MA, USA) [41]
- CAR T cells [42]
- Flotetuzumab (bispecific anti-CD123×CD3; MacroGenics, Rockville, MD, USA) [43]
- IMGN632 (anti-CD123; ImmunoGen, Waltham MA, USA) [44]

Isocitrate dehydrogenase 1 and 2

- Enasidenib (Idhifa[®]; Celgene Corporation, Summit, NJ, USA and Agios Pharmaceuticals, Cambridge, MA, USA) [45]
- Ivosidenib (Tibsovo[®]; Agios Pharmaceuticals, Cambridge, MA, USA) [46]

Other small molecule compounds

- HDAC inhibitors:
 - vorinostat (Zolinza[®]; Merck, Kenilworth, NJ, USA) [47–50]
 - panobinostat (Farydak[®]; Novartis, Cambridge, MA, USA) [51, 52]
 - romidepsin (Istodax[®]; Celgene Corporations, Summit, NJ, USA) [53–55]
 - SB939 (Pracinostat[®]; MEI Pharma, San Diego, CA, USA) [56]
 - SNDX 275 (Entinostat[®]; Syndax, Waltham, MA, USA) [57]
- BCL-2 inhibitor: venetoclax (Venclexta[®]; AbbVie-Genentech, North Chicago, IL, USA) [58–61]

*Not inclusive of all compounds that have been or are undergoing clinical study.

Abbreviations: AML, acute myeloid leukemia; BCL-2, B-cell lymphoma 2; CAR, chimeric antigen receptor; HDAC, histone deacetylase.

synthesis and/or chromosome segregation are regulated through checkpoint activation and cell-cycle arrest [92, 93]. This regulatory process involves multiple proteins, including cyclins, CDKs, and CDK inhibitors (CKIs), leading ultimately to CDK inhibition [94]. Mutations in CDKs and their regulators (cyclins and CKIs), as well as epigenetic repression of these genes, have been shown to be directly associated with deregulation of the cell cycle in multiple types of cancers [95, 96]. Through the cell cycle, cells divide and replicate following a precise and strictly regulated process. This is coordinated by the activation and degradation of heterodimeric protein complexes formed by catalytic serine/threonine CDKs, notably CDK2/4/6, and their regulatory counterparts, a subset of cyclins directly involved in driving the cell cycle. Regulatory cyclins include D-type cyclins (D1, D2, and D3), which bind preferentially to CDK4/6, and E-type (E1 and E2) and A-type (A1 and A2) cyclins, which bind to CDK2 [95–97]. CDK/cyclin activity is negatively regulated by two families of CKIs: the INK4 (p16Ink4a, p15Ink4b, p18Ink4c, and p19Ink4d, which inhibit the cyclin D-dependent CDK2/4/6) and Cip/Kip (p21waf1, p27kip1, and p57kip2, which inhibit CDK2/cyclin E or A) (Figure 1) [95, 96]. In

addition, cell-cycle regulatory proteins associate with each other through the retinoblastoma protein (pRb), which is phosphorylated by activated cyclin D–CDK4/6 complexes. This process regulates pRb-modulated availability of the transcription factor E2F: unphosphorylated pRb blocks the availability of E2F, while cyclin D–CDK4/6-mediated pRb phosphorylation releases E2F, triggering the transcription of early E2F-responsive genes, including cyclins E and A (Figure 2A–2B) [100]. The effect of alvociclib on cell-cycle progression has been linked to inhibition of several CDKs, including CDK1, 2, and 4/6 [68, 86–88]. The main molecular mechanisms that have been associated with the activity of alvociclib are summarized in Table 2 [49, 71, 73–75, 77, 89, 90, 94, 101–126].

In addition to its inhibitory effects on cell-cycle-related CDKs, alvociclib exhibits its most potent effects on CDK7 and CDK9, both of which are non-cell-cycle-related and play important roles in transcription and gene expression, including several genes that are critical for cell survival under stress [102, 105–107]. Both CDK7 and CDK9 target the carboxyl-terminal domain (CTD) of RNA polymerase II, controlling, through sequential phosphorylation of different residues, the transcription

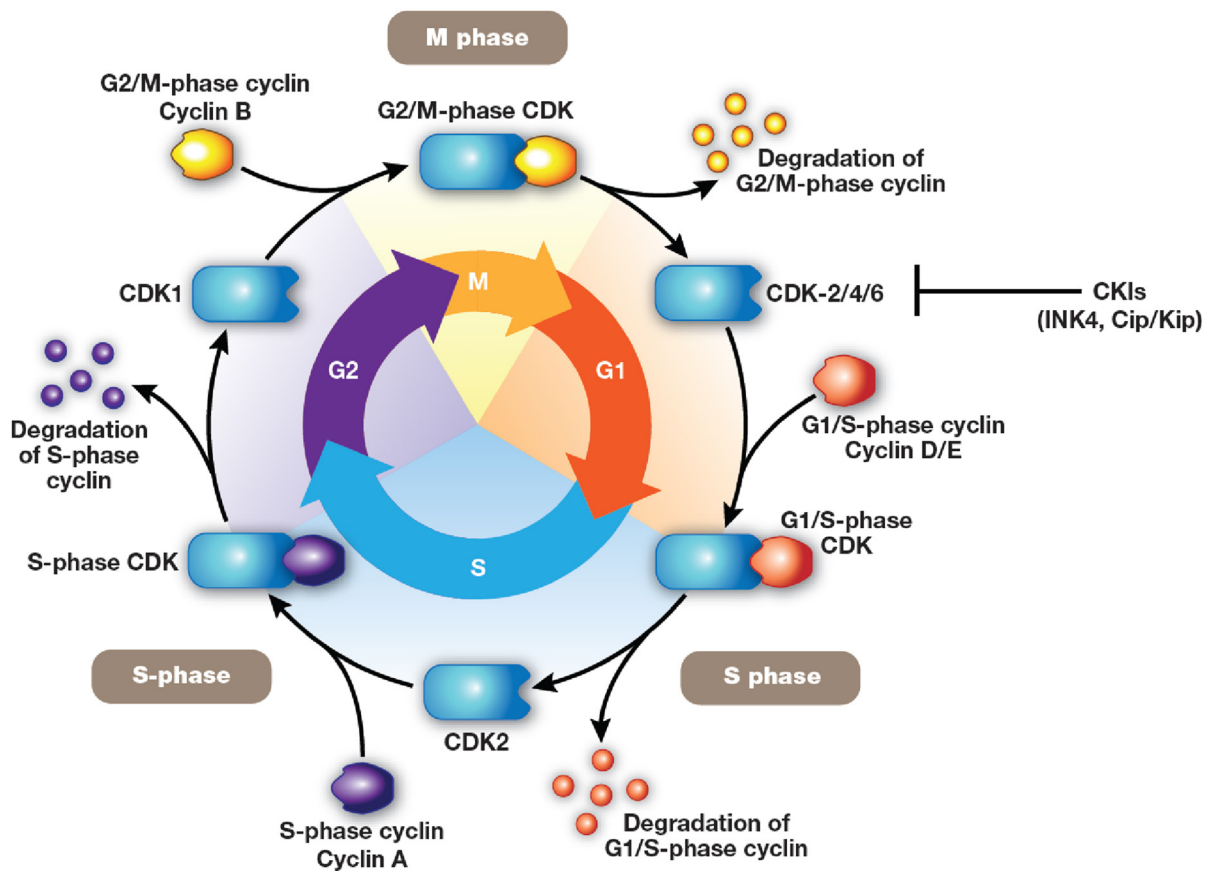


Figure 1: Cell cycle. Cells divide and replicate following a precise and strictly regulated process. Cell-cycle progression is coordinated by the activation and degradation of heterodimeric protein complexes formed by catalytic serine/threonine cyclin-dependent kinases (CDK; CDK2/4/6), and their regulatory counterparts (D-type cyclins D1, D2, D3; E-type cyclins E1 and E2; A-type cyclins A1 and A2). [95–97] The activity of CDK/cyclin complexes is negatively regulated by two families of CDK inhibitors: INK4 (p16Ink4a, p15Ink4b, p18Ink4c, p19Ink4d, which inhibit the cyclin D-dependent CDK2/4/6) and Cip/Kip (p21waf1, p27kip1, p57kip2, which inhibit CDK2/ cyclin E or A) [98, 99].

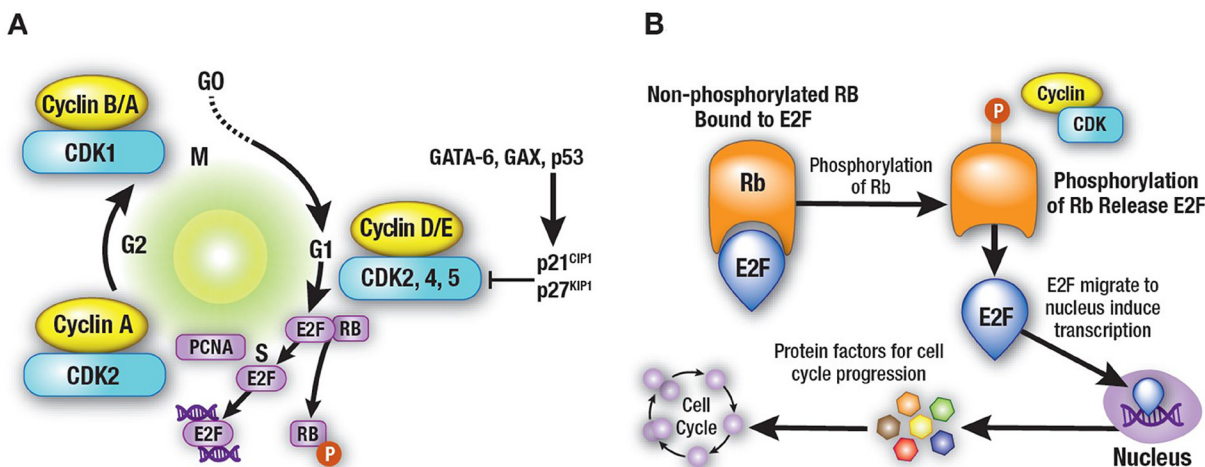


Figure 2: Cell-cycle regulatory proteins. (A) Cell-cycle regulatory proteins are associated with each other through the retinoblastoma protein (pRb), which is phosphorylated by the activated cyclin D–CDK4/6 complexes, a process that regulates pRb-modulated availability of the transcription factor E2F. (B) Unphosphorylated pRb blocks the availability of E2F, while cyclin D–CDK4/6-mediated pRb phosphorylation releases E2F, triggering the transcription of early E2F responsive genes, including cyclins E and A. [100] The effects of alvocidib on cell-cycle progression are linked to its ability of inhibiting several CDKs including CDK1, 2, and 4/6 [71, 89–91].

Table 2: Main molecular mechanisms involved in the activity of alvocidib**Modulation of cell cycle**

- Cell cycle arrest at the G1 phase through inhibition of cell cycle-related CDK1, CDK2, CDK4, and CDK6 [71, 89, 90, 94, 102, 103]
- CDKI p21^{CIP1} transcriptional inhibition. [49, 73, 103, 104]

Regulation of transcription

- Inhibition of non-cell-cycle-related CDK7 and CDK9 [103, 105–107]
- Potent alteration of the expression of genes involved in cell cycle, cell death, and transcriptional regulation, among others [108–110]

Effects on cell death–apoptosis pathways

- Mitochondrial-mediated cell death induction [75, 111]
- Regulation of MCL-1 [74, 112–114]
- Regulates the expression of other pro- and anti-apoptotic proteins including BCL-2-[115–121] and IAP-[77, 116, 122–126] family proteins

Abbreviations: BCL-2, B-cell lymphoma 2; IAP, inhibitor of apoptosis proteins; MCL, myeloid cell leukemia.

process at several stages including initiation, elongation, and termination [127, 128]. CDK7 and its associated regulatory proteins cyclin H and MAT1 are part of a complex within transcription factor IIH, which regulates RNA polymerase II during the initiation phase and during promoter clearance [129–131]. CDK9, on the other hand, is part of positive transcription elongation factor b (P-TEFb) and is modulated by its association with cyclins T1, T2a, and T2b, having a unique role in the regulation of RNA polymerase II during productive elongation [132–134].

Targeting gene transcription as a means of controlling the expression of critical proteins has been considered a potentially risky strategy because of nonselective effects that may impact both cancer and normal cells [135, 138]. However, recent studies have shown that a number of highly expressed genes that are either oncogenic (eg, MYC, MYCN, RUNX1) [137–140] and/or provide critical survival advantages (eg, MCL-1) [8] are highly dependent on continuous active transcription. Gene expression relies on *cis*-acting DNA sequences, namely transcription enhancers, which increase transcription independently of their orientation and distance relative to the RNA start site. These transcription enhancers are discrete DNA elements that contain specific sequence motifs with which DNA-binding proteins interact and transmit molecular signals to genes [141, 142]. To maintain adequate levels of short-life proteins such as MCL-1 in cancer cells, the continuous active transcription of the genes coding for these proteins is often driven by large sections of DNA that comprise multiple enhancers, named “super-enhancers” [143–145]. Although the activities of thousands of genes are controlled by enhancer elements, only those genes with especially prominent roles are controlled by super-enhancers [143]. These regions are densely populated by components of the transcription machinery (ie, in addition to transcription factors, co-factors, RNA polymerase II, and CDKs), including targets of alvocidib therapy CDK7, CDK8, CDK9, CDK12, and

CDK13 [143, 146, 147]. From a therapeutic standpoint, that most of the genes regulated by “super-enhancers” code for short half-life mRNAs and proteins makes targeting gene transcription a feasible approach in cancer therapy, as highly selective effects may be reached before a global transcriptional down-regulation is achieved [136].

ALVOCIDIB AND APOPTOSIS IN CANCER CELLS: REGULATION OF MCL-1

Dysregulation and evasion of apoptosis is one of Hanahan and Weinberg’s hallmarks of cancer [5, 88]. Cell death by apoptosis may occur through two major signaling pathways: the intrinsic (or mitochondrial) pathway and the extrinsic (or death receptor-mediated) pathway [148, 149]. Early studies provide evidence that exposure of human leukemia cells to alvocidib triggers apoptosis by the mitochondrial rather than the death receptor-mediated pathway [75, 111]. The intrinsic apoptotic pathway, following pro-cell death stimuli, is initiated by mitochondrial outer membrane permeabilization (MOMP) and the release of cytochrome c from the intermembrane space [150]. This process is controlled by the BCL-2 family of proteins [148], which are grouped into three classes: proapoptotic effector proteins, including BAX and BAK, which are responsible for MOMP; anti-apoptotic BCL-2 proteins, such as BCL-2, BCL-xL and MCL-1, which block MOMP; and the BCL-2 homology (BH)3-only proteins BID, BIM, BAD, BIK, HRK, PUMA, BMF, and NOXA, which either activate proapoptotic effectors and/or neutralize anti-apoptotic BCL-2 proteins [148, 151]. Multiple studies have investigated the BCL-2 family of proteins as therapeutic targets. The most advanced of these efforts led to the approval of the BCL-2 inhibitor venetoclax for patients with high-risk CLL [152]. In AML, venetoclax has shown preclinical activity [153], with

modest single-agent activity in relapsed/refractory AML [61]. However, preliminary clinical data on venetoclax in combination with DNA methyltransferase inhibitors or low-dose cytarabine have shown encouraging results [58, 59, 60, 154–155]. Venetoclax has shown activity in preclinical studies in acute lymphoblastic leukemia [156, 157] and is currently being investigated in pediatric and adult clinical trials. Because of the risk of TLS, prophylactic use of anti-hyperuricemics and hydration is recommended prior to the first dose of venetoclax [158].

Essential to the mechanism of alvocidib-induced anticancer activity is its effect on the expression of MCL-1, which has been shown to play a critical role in sensitizing cells to cell death [74, 112–114]. High levels of anti-apoptotic MCL-1 and other members of the BCL-2 family (eg, BCL-2, BCL-xL) have been shown to contribute not only to the development of some forms of cancer, but also to providing them with survival advantages and chemotherapy resistance [6–10, 159–161]. In fact, amplification of the MCL-1 gene is one of the most frequent somatic genetic events in human cancer, providing evidence of its central role in the pathogenesis of malignancy [159]. Studies examining the expression of BCL-2 family members, including MCL-1 in primary human hematopoietic subsets and leukemic blasts from patients with AML, have consistently shown high expression levels of MCL-1 transcripts [10]. In a functional *in vivo* study of Myc-induced murine AML with high levels of MCL-1, reduction of MCL-1 levels through haploinsufficiency abrogated AML development, supporting the critical role of MCL-1 in AML pathogenesis [10]. Similar observations in AML have shown that high levels of MCL-1, but not of other anti-apoptotic proteins such as BCL-xL, BCL-2 or BCL-w, are critical to the development and sustained growth of the disease [6]. It is noteworthy that alvocidib has been shown to induce the expression of the anti-apoptotic BCL-2 gene in leukemic blasts in adults with refractory AML [119]. However, expression of BCL-2 does not appear to have a major impact on alvocidib-induced lethality [75, 162]. Furthermore, alvocidib displays synergistic effects when administered with selective BH3 mimetic BCL-2 inhibitors (ABT-199 or venetoclax) in *in vitro* and *in vivo* models of AML [163].

Importantly, the differential effects of MCL-1 versus other apoptosis-related BCL-2 family members may reside in a newly identified function of MCL-1. In addition to its role in controlling and opposing cell death, which is related to its localization on the outer mitochondrial membrane, an amino-terminally truncated isoform of MCL-1 was found to be imported into the mitochondrial matrix where it facilitates normal mitochondrial function, membrane potential, ATP production, respiration, cristae ultrastructure, and maintenance of oligomeric ATP synthase [164]. These findings provide key information on how the diverse functions of MCL-1 may contribute

to cell homeostasis and function, supporting the evidence that high levels of MCL-1 in human cancers contribute to malignant cell growth and evasion of apoptosis [165]. One distinct difference between MCL-1 and other members of the BCL-2 family is its very short half-life, between 0.5 hours and 4 hours [8, 166], which makes it dependent on continuous and active gene transcription, an effect achieved (as mentioned above) through super-enhancer-driven transcription ultimately modulated by CDK9 [143, 146, 147].

Despite alvocidib showing potent clinical activity against blood cancers, patients develop primary or acquired resistance to treatment throughout their clinical course. To understand the mechanism of acquired resistance to alvocidib in leukemia, an alvocidib-resistant cell line was created in a CLL model [161]. The alvocidib-resistant cell line exhibited high transcriptional activity and increased CDK9 activity to promote RNA polymerase II activity, thereby increasing RNA transcription of alvocidib targets. The alvocidib-resistant cell line also exhibited increased transcription and stability of MCL-1. Of particular importance, knockdown of MCL-1 in the alvocidib-resistant cell line partially restored sensitivity to alvocidib. This suggests that the upregulation and stability of MCL-1, as well as enhanced CDK9 activity, are important components of acquired resistance to alvocidib [161]. The relationship between the level of MCL-1 expression and the response to alvocidib is being examined in a phase II study of patients with AML (NCT02520011).

Other proteins affected by alvocidib and critically involved in the regulation of apoptotic signaling include the inhibitor of apoptosis proteins (IAP) family, a group of eight structurally related proteins with the ability to suppress apoptosis, most notably X-linked IAP (XIAP), c-IAP1, c-IAP2, and survivin [167, 168]. Although c-IAP1 and c-IAP2 exert their inhibitory effects on cell death indirectly by functioning as E3 ubiquitin ligases promoting the ubiquitination of caspase-3 and -7 [169, 170], XIAP binds to and inhibits caspase-3, -7, and -9 [167]. Alvocidib has been shown to down-regulate XIAP at the transcriptional level [77].

CLINICAL DEVELOPMENT OF MCL-1 SMALL MOLECULE INHIBITORS

Several studies investigating the role that MCL-1 expression plays in cancer development and treatment have resulted in significant efforts to develop compounds, such as alvocidib, that may target this apoptosis-inhibitory protein. Approaches to down-regulate MCL-1 expression have been directed multiple ways: inhibiting its transcription via CDK9 inhibition, as is the case with alvocidib and other CDK inhibitors [113, 114]; at the translational level, as occurring in human leukemia cells exposed to sorafenib [171]; or by targeting protein-protein

interactions to directly affect MCL-1 anti-apoptotic activity [8, 172–174].

In addition to alvocidib, there are other MCL-1 inhibitors in development. The small molecule S63845 (Servier Laboratories, Suresnes, France and Novartis, Basel, Switzerland) [174] has been shown to bind with high affinity to the BH3-binding groove of MCL-1, resulting in apoptosis of MCL-1–dependent multiple myeloma, leukemia, and lymphoma cells [174]. In addition, S63845 has been shown to sensitize several solid cancer cell lines (including breast cancer and melanoma) to other therapeutic agents. The small molecule MCL-1 inhibitors AMG 176 (Amgen, Thousand Oaks, CA, USA) [175] and AZD5991 (AstraZeneca, Cambridge, UK) [176] are currently in phase I clinical evaluation (NCT02675452 and NCT03218683, respectively) and continue to accrue patients in the US. Other compounds under clinical study include MIK665 (NCT02992483) and S64315 (NCT02979366). Given the marked interest in MCL-1 inhibitors and the efforts currently underway in academic institutions and pharmaceutical laboratories, a summary of some of these studies has been recently published [172].

SUMMARY

Since its introduction to the field of cancer therapeutics, alvocidib has received much attention, resulting in an accumulation of knowledge and understanding of the mechanisms affecting cancer cell survival. This has led to the development of promising combination therapies against leukemia, including AML, where efficacious approaches are urgently needed. It is clear that alvocidib, by targeting the CDK9/MCL-1 axis and thereby interfering with one of the main pro-survival proteins, represents a unique compound in an area of research where much effort is being invested. Advances have been made in terms of identifying new strategies and schedules of administration that have greatly improved the clinical activity of alvocidib, notably as part of regimens such as ACM, where results supporting its further development have been recorded, especially in patients with newly diagnosed AML.

Author contributions

Tapan Mahendra Kadia contributed to the conception and design of the manuscript, collection and assembly of data, manuscript writing, and gave final approval for publication.

Hagop M. Kantarjian contributed to the conception and design of the manuscript, collection and assembly of data, manuscript writing, and gave final approval for publication.

Marina Konopleva contributed to the conception and design of the manuscript, collection and assembly

of data, manuscript writing, and gave final approval for publication.

ACKNOWLEDGMENTS AND FUNDING

Medical writing and editorial support were provided by Adelphi Communications, New York, NY and Ashfield Healthcare Communications, part of UDG Healthcare plc, Dublin, Ireland, and were funded by Boston Biomedical, Inc., Cambridge, MA. None of the named authors received any compensation for their contributions to this work.

CONFLICTS OF INTEREST

Tapan Mahendra Kadia: Consultant for AbbVie, Amgen, Jazz Pharmaceuticals, Genentech, Novartis, and Takeda; research funding from AbbVie, Bristol-Myers Squibb, Celgene, Jazz Pharmaceuticals, Pfizer, and Sanofi.

Hagop M. Kantarjian: Honoraria from AbbVie, Agios, Amgen, Immunogen, OrsineX, Pfizer, and Takeda; research funding from AbbVie, Agios, Amgen, Ariad, Astex, Bristol-Myers Squibb, Cyclacel, Immunogen, Jazz Pharmaceuticals, and Pfizer.

Marina Konopleva: Consultant for AbbVie, Genentech, F. Hoffman La-Roche; served as advisory board member for F. Hoffman La-Roche; holds shares from Reata Pharmaceuticals; honoraria from Amgen, AbbVie, and Genentech; research funding from AbbVie, Genentech, Eli Lilly, Cellectis, Calithera, Stemline, Threshold, Flexus Biosciences, Novartis, Ablynx, and Agios.

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